Engineering Sciences
ISSN: 1308 7231 (NWSAENS)
ID: 2017.12.1.1A0373

Status : Original Study
Received: October 2016
Accepted: January 2017

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http://dx.doi.org/10.12739/NWSA.2017.12.1.1A0373

AN OVERVIEW OF NANOTOXICOLOGY

ABSTRACT

Nanotechnology grows rapidly and has potential applications in many areas such as industry, agriculture, business, medicine etc. Since nanomaterials are used in daily life activities nowadays, research on the toxicity of nanoparticles gains more importance. Nanoparticles (NPs) have been studied for cell toxicity, immunotoxicity, and genotoxicity. This review reports a summary of recent researches on the toxicity of nanomaterials having different classes: metals and non-metals.

Keywords: Toxicity, Metal Nanoparticles, Non-Metal Nanoparticles, Nanotoxicology, Immunotoxicity

NANOTOKSİKOLOJİYE GENEL BAKIŞ

ÖZ

Nanoteknoloji hızla büyümekte ve günümüzde endüstri, tarım, tıp gibi bir çok sektörde kullanım alanı bulmaktadır. Nanomalzemelerin kullanımının günden güne artması, bu malzemelerin toksik özelliği ile ilgili yapılan çalışmaları daha da önemli hale getirmektedir. Hücre toksisitesi, immünotoksisite ve gen toksisitesi konuları, nanopartiküller için başlıca çalışma konularını oluşturmaktadır. Bu derleme, metal ve ametal olarak ana sınıflara ayrılmış nanomalzemelerin toksitisitesi üzerine yapılmış güncel çalışmaların bir derlemesini sunmaktadır.

Anahtar Kelimeler: Toksisite, Metal Nanopartiküller, Ametal Nanopartiküller, Nanotoksikoloji, İmmünotoksisite

How to Cite:
Yalçın Enis, İ., Küçükali Öztürk, M., Sezgin, H., and Ismar, E., (2017). An Overview of Nanotoxicology, **Engineering Sciences (NWSAENS)**, 12(1):57-65, DOI: 10.12739/NWSA.2017.12.1.1A0373.

1. INTRODUCTION

Nanomaterials include nanorods, nanotubes, nanofibers and nanoparticles which have one or more dimensions less than 100 nm. Although nanomaterials can be found in nature as a result of combustion, geological or biological processes, they can also be produced by engineers to obtain unique required properties. The increase in their usage creates concerns about adverse health effects and environmental risk. Generally, the exposure to engineered nanomaterials can be controlled, but it may cause unwanted exposures because of a large amount of production and wide application areas. Therefore, it is a reality that, the future of the nanomaterials depends on its hazards, relative to its benefits [1 and 2].

Nanotoxicology is a discipline that deals with the adverse effects of engineered nanomaterials on living organisms and ecosystems. In traditional toxicity, "the dose" defines "the poison". However, this point of view should be modified in nanotoxicology [2]. Generally, nanomaterial size, shape, surface chemistry, and degree of aggregation are key factors that influence the toxicity [3 and 4]. The size of nanomaterials influences the cellular uptake and response to nanomaterials, their distribution, and elimination from the body. Nanomaterials with small size have an exponential increase in surface area, making the surface more reactive to biological components [5 and 6]. Because of their small size, nanoparticles can easily get into the human body and reach the most sensitive organs [7 and 8]. Nanoparticles (NPs) may have interaction with different parts of the human body, some of which are; respiratory and gastrointestinal tract, cellular system, liver, spleen and kidneys, nerves, lymphatic and circulatory systems and derm [1]. Ultrafine colloidal silica particles have the ability to induce tissue damage and inflammation in comparison with fine colloidal silica while ultrafine carbon particles are more toxic than fine carbons [2]. Moreover, aluminum oxide NPs (AlONPs) in diameter of 30-40 nm possesses dose-dependent genotoxic properties [9].

Moreover, the dynamic behavior of nanomaterials is significant which can be changed when they interact with biological systems. Nanoparticle-protein coronas can be formed when the proteins attached to nanoparticles in biological systems [2]. The degradability of the nanomaterials is also crucial for acute and long-term toxicity. While nondegradable nanomaterials can accumulate in cells and cause detrimental effects, the biodegradable nanomaterials can undergo changes in cells and may lead to unexpected toxicity [6]. Ecotoxicology more specifically deals with the effects of nanomaterials on the ecosystem. Many organisms are not able to detoxify and metabolize engineered nanomaterial. Therefore, besides their benefits to human life, nanomaterials remain one of the most dangerous pollutants for the global system [2]. The use of nanomaterials is increasing day by day. Due to this fact, the toxicity of nanoparticles gains more importance. This review reports a summary of recent researches on the toxicity of nanomaterials having different classes such as metals and non-metals.

2. RESEARCH SIGNIFICANCE

Humans are under the influence of various nano-scale materials since their childhood [10]. Although the number of publications on the topic of nanomaterials has increased to a large extent since the early 1990s, the total number of papers on nanotoxicity is still less but in progress. Since the use of nanomaterials has the tendency to increase in daily life, the risk for human as well as the environment should be studied well to overcome the uncertainties [4]. This review focused on the importance of toxicity of nanoparticles, which have wide application area.

3. NANOPARTICLES AND THEIR TOXICITY

Toxicity of nanoparticles can be investigated in two categories: metal and non-metal nanoparticles.

3.1. Metal Nanoparticles

The most common metal nanoparticles that have toxic effects can be classified as aluminum oxide, titanium dioxide, silver and copper oxide. AlONPs are less toxic than other metal-based nanomaterials. However, AlONPs have been demonstrated to induce cell death by impairing cellular components, both *in-vivo* and *in-vitro* [11]. In a study of Park et al., three different types of AlONPs, α-AlONPs and γ-AlONPs, and aluminum oxide hydroxide nanoparticles (γ-AlOHNPs) were synthesized and their distribution and biological responses in vivo (5 and 10 $mg.kg^{-1}$) were compared. Then, their toxicity was investigated in six cell lines, which were obtained from the potential target organs of AlONPs with the help of using different four in vitro toxicity assessment tools. The results demonstrated that γ-AlOHNPs caused the highest toxicity. Thus, the presence of hydroxyl groups is an important factor in determining the toxicity of AlONPs [11]. In a study of Prakash et al., AlONPs which were synthesized using microemulsion hindered the growth and multiplication of the tested bacteria, including highly multiresistant bacteria (Klebsiella Pneumonia, Salmonella typhi, and Vibrio cholera).

Alumina nanoparticles were added to the cell membrane surface and it was seen that they disturbed cell's power function such as permeability and respiration [12]. However, Radziun et al. investigated the toxic effect of different concentrations of AlONPs in mammalian cells. These investigators employed EZ4U assay technique (cell proliferation and cytotoxicity) instead of MTT (a colorimetric assay for assessing cell metabolic activity) for cell viability assessment. It was found that AlONPs, at concentrations of 10, 50, 100, 200, and 400 $\mu g.ml^{-1}$ had no significant toxic effect on the viability of mammalian cells [13]. The result of a study by Kim et al. in which mouse lymphoma cells line was used, showed that aluminum oxide NPs (<50 nm) cause genotoxic effects in the form of DNA damage without any mutagenic effects [14]. Titanium dioxide (TiO_2) is used as an additive (E171) in food and pharmaceutical products.

TiO_2 that flows into the environment show low acute toxicity to aquatic organisms, thus with the long-term exposure it can induce a range of sub-lethal effects. TiO_2NPs can cause cell damage, genotoxic effects, inflammatory responses and changes in cell signaling [15]. TiO_2NPs (5-200 nm) possess toxic effects on immune function, liver, kidney, spleen, myocardium, glucose, and lipid homeostasis in experimental animals, hence they should be used with great care [15 and 16]. Wilson et al. showed that TiO_2NPs caused an increase in reactive oxygen species generation, and a decrease in mitochondrial membrane potential, suggesting mitochondrial damage. High levels of exposure (100 parts per million) killed two-thirds of such brain cells within one day. It was also found that it harms the cells' mitochondria, which may ultimately lead to cell death [17]. In a study of Grassian et al., mice were exposed to TiO_2 nanoparticles in a whole body exposure chamber 4 $hr.day^{-1}$ for 10 days. Toxicity in exposed mice was investigated by using total and differential cells, determination of total protein, lactate dehydrogenase (LDH) activity and inflammatory cytokines in bronchoalveolar lavage (BAL) fluid. Lungs were also evaluated for histopathologic changes. The results of this study showed that mice exposed to 0.77 or 7.22 $mg.m^{-3}$ nanoparticles indicated minimal lung toxicity. Mice exposed to 8.88 $mg.m^{-3}$ had alveolar macrophages in the BAL fluid compared with sentinels. However, the mice recovered by

week 3 post exposures [18]. In a study of Federici et al., organ integrity and the physiological effects of TiO_2 NPs in rainbow trout, resulted that TiO_2 NPs cause respiratory toxicity and disturbances to the metabolism of some trace elements like Zn and Cu in a few days [19]. Silver nanoparticles (AgNPs) are an important part of nanomaterials for a wide range of industrial and medical applications that have potential risks to human health [20]. Owing to its antibacterial, mothproofing and antistatic properties, AgNPs are used in textile industry [21]. AgNPs are effective biocides against bacteria, fungi, virii [22]. Although it is toxic, silver imposes lower toxicity to mammalian cells and higher toxicity to microorganisms, compared to other metals [23]. In a study of Ahamed et al., it was observed that AgNPs had toxicity in a variety of organs, including the lung, liver, brain, vascular system, and reproductive organs. AgNPs may cause induction of reactive oxygen species, oxidative stress, DNA damage and apoptosis [20].

Burd et al. studied the cytotoxicity of five commercially available silver-based dressings and they found out that three of them have a significant cytotoxic effect on human fibroblasts and keratinocytes [24]. Hussain et al. investigated the toxic effect of metal and metal oxide nanoparticles on rat liver derived cell line. Results showed that while lactate dehydrogenase leakage increased, mitochondrial function, decreased significantly in cells which are treated with AgNPs. Besides, cells that are exposed to higher dose nanoparticles show cellular shrinkage and abnormal sizes [25]. In another study, Gort et al. exposed silver nanoparticles to Drosophila eggs with concentrations ranging from 10 ppm to 100 ppm to investigate the size, chemistry, and agglomeration of the silver particles using transmission electron microscopy, X-ray photoelectron spectroscopy, and dynamic light scattering. The results indicated that, nanoscale silver particles (<100 nm) are less toxic to Drosophila eggs than silver particles of conventional (>100 nm) size [26].

The effect of concentration of AgNPs on toxicity was also studied in a study of Asharani et al. In this study the AgNPs were added to embryos and it was specified that nanoparticles caused some damage in the skin of the embryos. Additionally, it was observed that the deposition of nanoparticles inside the nucleus of the cells can cause DNA damage and chromosomal aberrations. Nanoparticle deposition in the central nervous system has negative effects on controlling the cardiac rhythm, respiration and body movements. Moreover, the exposure of AgNPs caused hyperemia in different parts of the body thus edema and necrosis occur [27]. Copper oxide NPs (CuNPs) are used in semiconductors, antimicrobial reagents, heat transfer fluids, and intrauterine contraceptive devices [28]. In a study of Ahamed et al. negative effects of copper oxide nanoparticles such as cytotoxicity, oxidative stress, DNA damage were investigated. The results indicated that exposure to CuNPs caused DNA damage in human lung epithelial cells by lipid peroxidation and oxidative stress [29]. Dozens of mice were treated with nano-copper and housed in metabolism cage. When nano-copper reacts to the acid substance in the stomach, lots of proton ions are eliminated [30].

3.2. Non-Metal Nanoparticles

Growing usage of nanoparticles (NPs) such as carbon-based nanomaterials, polymeric nanoparticles, and silica particles increase the concerns about possible hazardous effects on health and environment [8]. Carbon-based nanomaterials have been used in a wide range; including carbon nanofibers, carbon nanotubes, and carbon nanoparticles. The growing interest of carbon-based nanomaterials comes

with environment and health concerns. Generally, carbon-based nanomaterials lead to proliferation inhibition and cell death and the precise mechanisms of cell death are still indistinct, however, carbon nanotubes are less toxic than carbon fibers and nanoparticles [31]. It is known that CNTs promote allergic, acute and chronic inflammatory, fibrogenic and tumorigenic responses. Production and application of CNT-based nanoproducts seem to increase in the future. The presence of CNTs in the environment, increase either in the form of product wear, disposal, or manufacturing. [32]. Toxicity of carbon nanotubes investigated on mouse via inhalation and study parameters set as translocation of NPs from lungs to blood circulation. According to the results, significantly less translocation and accumulation were achieved with 80 nm than 20 nm particle size [4]. Toxicological assessments of as-grown Single-walled Carbon Nanohorns (SWNHs) investigated by Miyawaki et al., under different exposure pathways. Results indicated that SWNHs have low toxicity because SWNHs not include metal catalyst [33].

Magrez et al. indicated that carbon nanotubes have higher toxicity when their surface functionalized with a carbonyl (C=O), carboxyl (COOH), and/or hydroxyl (OH) groups [31]. In a study of Lee et al., the effect of Multi Wall Carbon Nanotubes (MWCNTs) on workers' health was presented in a workplace where MWCNTs are manufactured. The results showed that exhaled breath condensate of workers includes higher levels of oxidative stress markers and higher blood molybdenum than office workers [34]. Among the different types, MWCNT Mitsui 7 is classified as a carcinogen [32]. In another research on rodent animal models and in vitro cell cultures, it was described by Hardman et al. that quantum dots have a possible risk of human and environmental issues. Furthermore, the toxicity of quantum dots depends on their size and physicochemical properties [35].

Biodegradable or polymeric NPs can be used in drug delivery in cancer chemotherapy. These NPs are also expanded in the encapsulation of various molecules to improve nanomedicine providing sustained release and good biocompatibility with cells and tissues [36]. Moreover, they have the potential to be successfully employed in the encapsulation of peptides, nucleic acids, and proteins. They are also deemed as non-toxic, nonimmunologic, non-inflammatory and do not activate neutrophils. Grabowski et al. used Poly-(D, L-lactide-co-glycolide) as a nanosystem for targeted delivery of drugs and other molecules. It was reported that toxicity of Poly-(D, L-lactide-co-glycolide) based nanosystem is too low [37]. In another study Voigt et al. used poly butyl cyanoacrylate nanoparticles (PBCA NPs) for a drug delivery system, which can cross the blood–brain barrier (BBB). Cells were exposed to PBCA NPs in vitro and in vivo and observed their life and death assays. In vitro, dose-dependent cell death was found especially in high doses. However, the in vivo experiments no NP-induced neuronal death was monitored with particles which were toxic at the high dose in vitro [38].

Silica or silicon dioxide (SiO_2) can be found in natural and synthetic forms. Since natural amorphous silica is considered less harmful, most of the synthetic silica used in a large variety of applications are in amorphous forms. However, the toxicity of silica is mainly determined by its crystallinity [39]. According to International Agency for Research on Cancer (IARC), crystalline silica polymorphs are defined under a group of sufficient evidence for the carcinogenicity to experimental animals and to humans, while amorphous silica was classified in inadequate evidence for carcinogenicity [40]. Synthetic amorphous silica nanoparticles (SNPs) are preferably used in additives to cosmetics, drugs, printer toners, varnishes, and food. Moreover,

SNPs are used in biomedical and biotechnological applications such as cancer therapy, DNA transfection, drug delivery, and enzyme immobilization [41 and 42]. Ultrafine particles (<0.1 µm) have been demonstrated to cause greater inflammatory responses and particle-mediated lung diseases than have fine particles (<2.5 µm) per given mass [43 and 44]. In a study of Chen and von Mikecz et al., SiO_2 particles between 40 nm and 5 µm were applied to epithelial cells in culture. Although all sizes of SNPs penetrated the cytoplasm, nuclear localization was examined significantly in SiO_2 nanoparticles (40 and 70 nm) treated cells. Fine and coarse SiO_2 particles (0.2-5 µm) were found located in the cytoplasm and accumulated around the nucleus, forming nuclear indentations [45].

4. CONCLUSION

The field of nanotechnology has expanded day by day since nanomaterials are used in many applications in our daily life. Human exposure to nanomaterials is unavoidable. They can easily get into the body through the lungs or other organs by food, medicine and have an impact on organs, tissues, and cells. They have toxic effects such deformation and inhibition of cell growth, DNA damage, and chromosomal aberrations, etc. Because of this, the use of nanomaterials should be controlled to minimize their negative effects. Safe nanomaterials should be preferred to apply in existing areas in the future.

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